Maastricht University

# The impact of the ‘Western Diet’ on emotional, social and cognitive behaviours as revealed by a study on conventional and serotonin transporter-deficient mice

Citation for published version (APA):

Veniaminova, E. (2020). The impact of the ‘Western Diet’ on emotional, social and cognitive behaviours as revealed by a study on conventional and serotonin transporter-deficient mice. [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20200305ev

**Document status and date:**
Published: 01/01/2020

**DOI:**
10.26481/dis.20200305ev

**Document Version:**
Publisher's PDF, also known as Version of record

**Please check the document version of this publication:**

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

**General rights**
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

**Take down policy**
If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 05 May. 2023

## Valorization

*Relevance for society*

Western-style foods consumption has been increasing steadily since the 1950s, especially in Western-culture countries. Due to a growing economy, higher income and faster pace of life, rates of Western diet consumption are also increasing nowadays in countries where such foods were never part of the traditional culture. Western diet is associated with metabolic disorders, such as obesity, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Worldwide, the estimated prevalence for obesity and NAFLD is around 650 million and for type 2 diabetes more than 500 million people. The WHO anticipates that worldwide deaths from diabetes will double by 2030.

Metabolic disorders are also often associated with increased risk of psychiatric disorders, including mood disorders, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). ASD and ADHD are complex neurodevelopmental disorders with the prevalence estimated 7% and 2% respectively, thus affecting more than 100 million people in the world. ASD may significantly limit the capacity of an individual to participate in society. Those affected may not be able to conduct day-to-day activities and require life-long care and support. Both ASD and ADHD negatively influence the person's educational and social attainments. These disorders cooccur

with a high frequency with each other as well as with affective disorders such as depression.

Increasing prevalence of ASD and ADHD suggests an important role of environmental factors, including nutrition, in the development of these disorders. While adverse reactions to foods have often been reported in children with ASD or ADHD, the impact of diet on ASD/ADHD associated behaviours in adulthood is much less well understood. Our study showed that in adult female mice, feeding with the Western diet induced behaviours phenomenologically similar to the behaviours associated with human ADHD and ASD. Thus, this work provides a rationale for future clinical studies on the effects of nutrition on ADHD and ASD syndromes in adulthood. Based on our results, it can be suggested that dietary interventions may lead to symptom relief in patients with ASD or ADHD, which will decrease costs associated with disability and health management.

We also found metabolic changes and signs of neuroinflammation and oxidative stress in the brains of mice fed with the Western diet. These data suggest that compounds with anti-inflammatory and antioxidative properties might be useful to ameliorate symptoms in cases ASD or ADHD that cooccur with metabolic disorders such as type 2 diabetes or NAFLD. The main molecular targets reported in this study are toll-like receptor 4 (Tlr4) and peroxisome proliferator-activated receptor gamma (PPAR$\gamma$). Agonists and

antagonists of these receptors are now being studied in relation to diabetes, obesity, inflammatory disease treatment, and our work may further increase the interest of the industry in these compounds by proposing new applications.

Decreased activity of serotonin transporter (SERT), which occurs in a large percentage of people due to the 5-HTTLPR polymorphism in the SERT gene, was extensively discussed as a factor of genetic predisposition to affective and neurodevelopmental disorders. Current work demonstrated that mice with partial Sert deficiency displayed a resilience to dietary-induced abnormalities in glucose tolerance, Tlr4 brain expression and hippocampus-dependent behaviour, aberrations that were present in mice with complete Sert deficiency and wild type animals after feeding with the Western diet. Based on our findings, it seems important to further study the consequences of interaction between adherence to a certain dietary pattern and the 5-HTTLPR polymorphism in humans, which might increase the need for genotyping services. Based on the genotype, further dietary counseling services as well as pharmacotherapy, such as use of compounds targeting TLR4, PPARγ or SERT might be advised.

*Target groups*

We consider our target groups could be 1) individuals with high adherence to the Western dietary pattern or patients with metabolic

disorders, 2) adult patients with ASD, ADHD and depression as well individuals with high genetic risk for these disorders.

*Activity / Products*

Our findings highlight the importance of future clinical investigation of the possible effects of the Western diet in those with a high susceptibility to, or having been diagnosed with, ASD, ADHD and depression. Dietary recommendations in combination with 5-HTTLPR polymorphism genotyping might be suggested for these groups. In some cases, pharmacotherapy using inhibitors/antagonists of TLR4 and agonists of PPARγ might be used.

*Innovation*

The work presented herein has been innovative in various regards. First, we have shown that the Western diet mice can evoke behaviours reminiscent of ASD and ADHD symptoms, as well as impairment of emotionality in a mouse model. In particular, our studies were among the first to show that in adult mice, Western diet alters social behaviour, which is known to be affected both in ASD and ADHD. This result suggests dietary interventions as a promising treatment approach in adult patients with ASD and ADHD. Then, our model of the three-week Western diet feeding provides an opportunity to study behavioural and brain changes associated with metabolic syndrome as well as possible pharmacotherapy at low labor and time

costs. Much longer periods of diet feeding have been employed routinely elsewhere in similar studies, leading to serious obesity. Further, we extended the knowledge of the Western det consequences on behavioural and brain molecular parameters in female mice, while in the past, predominately male rodents were used for this purpose. We also suggested important contributions of neuroinflammation, oxidative stress and altered Sert functioning in the discussed behavioural changes, which may direct pharmacotherapy development. And, finally, we investigated effects of the Western diet on metabolic, behavioural and molecular parameters in female mice with complete and partial deficiency of Sert. This has not been shown before, but is relevant to the human context regarding the 5-HTTLPR polymorphism, which also results in decreased SERT activity. We found that complete genetic Sert inactivation exacerbated metabolic alterations, neuroinflammation and behavioural consequences of the Western diet feeding in aging mice. On the contrary, mice with partial genetic Sert deficit displayed a "rescued" phenotype in dietary-induced abnormalities in glucose tolerance, Tlr4 brain expression and hippocampus-dependent behaviour, that was shown for the first time.

*Implementation*

Results of our study are relevant for scientific and medical communities and for the general public. From an academic perspective,

results were presented at national and international conferences (8 oral and 3 poster presentations at the conferences including "12th Goettingen Meeting of the German Neuroscience Society", "20th EURON PhD Days", and "19th WPA World Congress of Psychiatry") and were or will be published in peer-reviewed international journals. Being a part of Eat2beNice project (Horizon 2020 EU Research and Innovation programme, grant No. 728018), the study was presented in the project reports and in the New Brain Nutrition Blog (newbrainnutrition.com/blog, blogs: "Why do we use mouse models in diet research?", "Nutrition and Psychiatry: experience of attending the 19th WPA World Congress of Psychiatry"). Our model of the Western diet feeding in mice is currently being used by colleagues from the food industry and for investigating a 'healthy' meat product.